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Fibroblast Growth Factor 23 and Sudden Versus Nonsudden Cardiac Death: The Cardiovascular Health Study

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Abstract

Background—Elevated fibroblast growth factor 23 (FGF-23) concentrations are associated with greater risk of cardiovascular events and mortality, especially among people with chronic kidney disease (CKD). Since individuals with CKD are at an increased risk of sudden cardiac death (SCD), we sought to understand whether FGF-23 is a stronger risk factor for SCD versus non-SCD.

Study Design—Cohort study.

Setting & Participants—3,244 participants in the community-based Cardiovascular Health Study, aged 65 years or older.

Predictor—Plasma FGF-23 concentrations.

Outcomes—We assessed SCD and non-SCD in these analyses. SCD was rigorously adjudicated and was defined as a sudden pulseless condition of cardiac origin in a previously stable person occurring out of hospital or in emergency department.

Measurements—We estimated associations of baseline FGF-23 concentrations with SCD and non-SCD using Cox proportional hazards models after adjustment for demographics, cardiovascular risk factors, comorbidities, and kidney function. We also tested whether associations differed by CKD status.

Results—During a median follow-up of 8.1 years, there were 118 adjudicated SCD and 570 non-SCD events. After multivariable adjustment for demographics, cardiovascular risk factors, comorbidities, and parameters of kidney function, higher FGF-23 concentrations were an independent risk factor for non-SCD (HR [per doubling], 1.17; 95% CI, 1.06-1.30). Elevated FGF-23 concentrations, however, were not independently associated with SCD (HR [per doubling], 1.07; 95% CI, 0.85-1.35). In stratified analysis by CKD status (36.5% of cohort), doubling of FGF-23 concentrations was independently associated with non-SCD (adjusted HR, 1.26; 95% CI, 1.10-1.45). A similar magnitude of association was observed between FGF-23 and SCD among the CKD subgroup; however, it was not significant (HR, 1.20; 95% CI, 0.89-1.62).

Limitations—Limited power to detect moderate-sized effects between FGF-23 and SCD in both the primary and stratified analyses.

Conclusions—In this population-based study, FGF-23 elevations were independently associated with non-SCD. Among individuals with CKD, the associations between FGF-23 and SCD and non-SCD were similar.

Keywords

fibroblast growth factor 23 (FGF-23); chronic kidney disease (CKD); sudden cardiac death (SCD); non-SCD; cardiovascular event; cardiovascular mortality; fatal arrhythmic event; renal function; Cardiovascular Health Study (CHS); cohort study

Fibroblast growth factor 23 (FGF-23) is a hormone that is produced in osteocytes and regulates phosphorus and 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) metabolism. In the kidney, it induces renal phosphorus excretion and inhibits conversion of 25-hydroxyvitamin D to the active hormone $1,25(\text{OH})_2\text{D}$.¹ Elevations in FGF-23 concentrations are believed to

occur as a physiologic response to maintain normal serum phosphorus levels. As a result, FGF-23 concentrations rise progressively in kidney disease as the capacity for phosphorus excretion declines.² These compensatory changes maintain normal serum phosphorus levels by inducing its excretion and suppressing 1,25(OH)₂D synthesis. Despite this physiologic response, clinical studies have demonstrated that higher FGF-23 concentrations are strongly and independently associated with all-cause and cardiovascular mortality especially among individuals with chronic kidney disease (CKD).³⁻⁷

Since individuals with CKD are at an increased risk of arrhythmic complications and sudden cardiac death (SCD),^{8,9} we sought to understand whether FGF-23 is a stronger risk factor for sudden versus non-SCD. In experimental models FGF-23 induces left ventricular hypertrophy (LVH), and it is an independent predictor of congestive heart failure (CHF).^{3,7,10,11} Because LVH and CHF are well-known predictors of SCD and have been included in arrhythmic risk stratification algorithms,¹² we hypothesize that FGF-23 is an independent risk factor for SCD. Identifying unique risk factors for SCD is fundamental for the design of targeted preventive and treatment strategies. We evaluated serum concentrations of FGF-23 as a novel risk marker of adjudicated SCD and non-SCD events in a community-based cohort of the elderly.

METHODS

Study Population

The Cardiovascular Health Study (CHS)¹³ is a community-based study of cardiovascular disease risk in ambulatory older adults initiated by the National Heart, Lung and Blood Institute (NHLBI). The CHS recruited participants from Medicare eligibility lists in Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA. To be eligible, persons had to be aged 65 years or older, not institutionalized, expected to remain in the current community for at least 3 years, not under active treatment for cancer, and able to provide written informed consent. The initial 5201 participants were enrolled from January 1989 through June 1990; an additional 687 predominantly black participants were recruited in 1992-1993. In-person examinations were performed annually through 1998-1999 and again in 2005-2006. Telephone interviews were conducted semiannually from 1989 to 1999 and biannually thereafter. We measured FGF-23 concentrations at the 1996-1997 study visit, because it was the first visit at which urine albumin-creatinine ratios (ACRs) were measured. Among 3,406 individuals who participated in the 1996-1997 visit, we excluded those with insufficient blood specimens for FGF-23 measurement (n=69), and those missing creatinine (n=1) or ACR (n=92) readings, resulting in a final analytic sample of 3,244 participants for this analysis. The institutional review boards at all the relevant sites provided approval for this protocol. Finally, this protocol was implemented according to the Declaration of Helsinki.

Information on baseline confounders was obtained at the 1996-1997 study visit concurrent with FGF-23 measurements and included age, sex, race, self-reported health status, and cardiovascular disease risk factors including hypertension (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90mmHg, or use of anti-hypertensive medications), diabetes (fasting glucose ≥ 126 mg/dL or use of anti-glycemic medications or insulin),

smoking (current, former, or never), body mass index, total cholesterol, and use of lipid lowering medications. A 12-lead ECG was also performed. Cystatin C concentrations were measured using a BN II nephelometer (Siemens; www.siemens.com).¹⁴ Based on the recently published guideline from KDIGO (Kidney Disease: Improving Global Outcomes), we defined CKD using either a cystatin C–based estimated glomerular filtration rate <60 ml/min/1.73 m² or albuminuria (ACR ≥ 30 mg/g).¹⁵

FGF-23

Fasting (8-hour) EDTA specimens collected at the 1996-1997 study visit were stored at -70° Celsius until 2010 when they were thawed and measured for FGF-23 using a carboxy-terminal ELISA kit (Immutopics, www.immutopicsintl.com).^{3,16} Our estimates of the intra-assay and inter-assay coefficients of variation (CVs) ranged from 7.4 and 10.6%.

Outcomes: SCD and Non-SCD

Sudden cardiac death was defined as a sudden pulseless condition of cardiac origin in a previously stable person occurring out of the hospital or in the emergency department. For unwitnessed deaths, the participants must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest. These definitions concur with those proposed by the NHLBI working group on SCD.¹⁷ These cases could not have life-threatening, noncardiac comorbidities or be under hospice or nursing home care. A non-SCD event was defined as any cardiovascular death that was not adjudicated as a SCD event.

The adjudication process was composed of multiple steps. A specialized committee in CHS adjudicated the cause of death. All out-of-hospital cardiac deaths were then reviewed to identify whether the event was a sudden or non-SCD. Comprehensive data were gathered on cardiovascular deaths from hospital records, physician interviews, next of kin and/or witnesses, death certificates, and autopsy reports when available. Survivors or successfully resuscitated events were not included in the definition of SCD. A second physician conducted a blind review of a sample of 70 potential cases with an 88% inter-reviewer agreement and a κ value of 0.74 for SCD.¹⁸

Statistical Methods

We compared baseline characteristics of participants across FGF-23 quartiles using either χ^2 or ANOVA tests. We estimated the associations between FGF-23 and both SCD and non-SCD using Cox proportional hazards regression models. We evaluated FGF-23 as a continuous predictor variable to maximize statistical power. Given its right skewed distribution, FGF-23 levels were log₂ transformed, which facilitated interpretation of hazard ratios (HRs) “per doubling” of FGF-23 concentrations. In companion analyses we assessed associations by FGF-23 quartiles allowing the lowest quartile to serve as the reference category. In both cases, an initial model adjusted for age, sex, and race. A second model added cardiovascular risk factors and comorbidities (diabetes, hypertension, smoking, heart failure, and myocardial infarction), and alcohol use. A final model added eGFR and ACR. For each of the two outcomes, we also stratified patients by CKD status and evaluated an

FGF23*CKD interaction term in the final adjusted model for both the SCD and non-SCD outcomes.

The analyses evaluating associations between FGF-23 and SCD were repeated using a competing risk framework. In particular, since the Cox proportional hazards model treats non-sudden causes of death simply as indications to censor under an assumption of noncompeting risks, we repeated our analyses using a competing risk approach in which non-SCD and noncardiovascular death are treated as simultaneous competing risks.¹⁹ In addition, given the limited number of SCD events, SCD was not a competing risk for non-SCD. S-Plus, release 8.0 (Insightful Inc, Seattle, WA), and SPSS statistical software, release 15.0 (SPSS Inc, Chicago, IL), were used for the analyses. A P-value <0.05 was considered statistically significant.

RESULTS

Among the 3244 participants, the mean age was 78 ± 5 years at baseline and 60% were women. The mean eGFR was 71 ± 19 ml/min/1.73m², and the median urine ACR was 8.9 (interquartile range, 4.7-20.4) mg/g. The distribution of FGF-23 was right skewed with a median 70 (interquartile range, 53-99) relative units (RU)/ml. In comparison to participants with FGF-23 concentrations in the lowest quartile, those with higher levels were older and more frequently women and white (Table 1). Participants with higher FGF-23 concentrations also had a higher prevalence of most traditional cardiovascular disease risk factors, more LVH and a shorter QT interval on baseline ECG. Although individuals in the highest FGF-23 quartile had a higher prevalence of ECG-based LVH compared to those in the lower quartiles, the overall LVH burden was low (Table 1). Higher FGF-23 concentrations were also associated with a lower eGFR and higher ACR.

The unadjusted Spearman correlations of FGF-23 with eGFR and ACR were -0.42 and 0.20, respectively ($p < 0.001$ for each). Spline functions showed that the relationships of eGFR and ACR with FGF-23 were independent of each other.

We identified 118 SCD events over a median follow-up of 8.1 ± 3.2 years (incidence rate, 4.5 per 1000 person-years). The annualized incidence of SCD increased across FGF-23 quartiles (Figure 1). Specifically, the SCD incidence rate was 0.3% per year among individuals with FGF-23 concentrations in the lowest quartile and 0.7% per year among participants in the highest FGF-23 quartile. When evaluating FGF-23 as a continuous predictor variable, each doubling of FGF-23 was associated with approximately 26% higher risk of SCD after adjustment for demographics, traditional cardiovascular risk factors, and comorbidities. These estimates, however, were attenuated markedly after adjustment for eGFR and ACR and were rendered no longer significant (Table 2). Similarly, no independent associations were observed between FGF-23 and SCD in the competing risk analysis (Table S1, available as online supplementary material).

We adjudicated 570 non-SCD events over the follow-up period (non-SCD incidence rate, 21.7 per 1000 person-years). The annualized incidence of non-SCD increased across FGF-23 quartiles (Figure 2). The highest FGF-23 quartile was an independent risk factor for

non-SCD and a doubling in FGF-23 concentrations was associated with a 17% increased non-SCD risk after adjustment for demographics, traditional cardiovascular risk factors/ comorbidities, eGFR and ACR.

A pre-specified stratified analysis by CKD status demonstrated that over one-third (n=1183; 36.5%) of this cohort had CKD defined as an eGFR <60 ml/min/1.73m² or ACR ≥30 mg/g. Each doubling of FGF-23 level was associated with a 34% higher SCD risk in the CKD subgroup after multivariable adjustment for demographics and cardiovascular comorbidities (Table 3). Further adjustment for urine ACR and eGFR attenuated the risk and rendered the association no longer statistically significant within the CKD subset in both the primary and competing risk analysis (Table S2). FGF-23 concentrations, however, were associated with non-SCD after multivariable adjustment (Table 3). No associations were observed between FGF-23 and either SCD or non-SCD in participants without CKD even in the unadjusted model (*P* values for interaction for SCD and non-SCD are 0.5 and 0.02, respectively).

DISCUSSION

After analysis of 570 non-SCD and 118 SCD events in this population of community-based elderly participants, higher concentrations of FGF-23 were independently associated with non-SCD events only. Our results show that FGF-23 was not an independent risk factor for SCD. The FGF-23 and non-SCD association was stronger among participants with baseline CKD compared to those without CKD. In addition, among the CKD subgroup, the estimate of risk for SCD was similar to that of non-SCD; however, adjustment for the severity of kidney disease including eGFR and ACR attenuated the risk for SCD such that it was no longer significant.

Sudden and non-sudden cardiac death events share many common risk factors, and limited studies have evaluated the specific pathways implicated in each outcome. The findings from these analyses suggest that the excess cardiovascular mortality observed among elders with elevated FGF-23 concentrations is unlikely to be attributable to fatal arrhythmic events. Instead, non-SCD events, which often occur through conditions such as progressive heart failure or stroke, comprise the majority of cardiovascular deaths. Previous studies have demonstrated that FGF-23 is a stronger risk factor for CHF than atherosclerotic events.^{3,7} These studies may help to explain the lack of an independent association between FGF-23 and SCD in our population-based sample since most SCD events in the community are associated with MI and atherosclerotic complications.¹² In addition, although CHF and LVH are risk factors for ventricular fibrillation, these conditions may also result in progressive pump failure, mechanical dysfunction and a gradual clinical decline that eventually results in non-SCD.

Consistent with previous studies, our findings demonstrate independent associations between FGF-23 concentrations and non-SCD among individuals with CKD. Chronic kidney disease is closely linked to high FGF-23 levels, and multiple studies have demonstrated bidirectional associations. In particular, FGF-23 concentrations are known to rise early in the course of CKD.³ Furthermore, recent population-based studies suggest that FGF-23 concentrations are associated with a significantly increased risk of developing

ESRD.²⁰ These complex, inter-related processes are associated with other systemic conditions that may provide insight into why the combination of high FGF-23 levels and CKD increase the risk of non-SCD.

Recent experimental evidence suggests that sympathetic activation induces FGF-23 expression in a circadian-dependent pattern.²¹ Kidney disease and increased afferent activity are also associated with increased sympathetic activity.²² As such, it is conceivable that higher sympathetic activity mediates the link between CKD and FGF-23. This activation also increases myocardial mass and contributes to LVH, left ventricular enlargement, and CHF.²³⁻²⁵ CKD is also characterized by down regulation of klotho in the kidney and parathyroid glands.^{26,27} Binding of FGF-23 to the FGF receptor in the absence of its co-receptor klotho has been shown in animal models to result in adverse cardiac remodeling including LVH,¹⁰ which may subsequently result in both mechanical pump failure and arrhythmias.

The association observed between FGF-23 and non-SCD could be mediated by low levels of the active vitamin D hormone. Both FGF-23 and CKD inhibit production of 1,25(OH)₂D.^{1,28} The PRIMO (Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity in Chronic Kidney Disease Stage 3/4) Study evaluated supplementation with a 1,25(OH)₂D analog, paricalcitol, on cardiac structure and events.²⁹ Although therapy in this CKD population did not alter left ventricular measures, paricalcitol therapy reduced the number of heart failure hospitalizations. These findings suggest that the combination of high FGF-23, CKD, and low vitamin D may result in a higher risk for decompensated heart failure symptoms and subsequent hospitalizations and not fatal arrhythmic complications.

Strengths of this study include the relatively large sample size; evaluation of an older community-living population at higher risk for SCD; concurrent availability of FGF-23, eGFR, and ACR; and adjudicated SCD and non-SCD events. Despite these and other strengths, several limitations of the current study should also be considered. We had nearly five times more non-SCDs compared to SCDs in our analyses. The relatively small number of definitive SCD cases in these analyses reduced the power necessary to detect moderate-sized effects. As such, we may have been limited in finding independent associations between FGF-23 and SCD in the entire cohort and the CKD subgroup. In addition, the rigor and specificity of our adjudication protocol was likely to miss SCD events that had occurred in the CHS. Our adjudication protocol was based on ascertaining clinical records and next-of-kin interviews that indicated a sudden, out-of-hospital death in a previously stable individual.¹⁷ Previous, experimental studies also suggest that the sudden nature of death in a previously stable individual is likely attributable to fatal arrhythmias.³⁰ Although the optimal definition for identifying fatal arrhythmias would require a witnessed collapse, cardiac rhythm monitoring, and autopsy data, it is not feasible to have this degree of phenotyping in a large epidemiologic study. Because the CHS consisted solely of elderly persons, it is unknown whether these results generalize to younger persons. In addition, serum phosphate and vitamin D levels were not measured at the time of FGF-23 measurements in this analysis. As such, potential confounding due to disturbances in these other mineral metabolism measures cannot be evaluated. Finally, serial echocardiographic studies were not assessed in this study. Thus, we cannot evaluate whether changes in left

ventricular structure and function mediate the association observed between high FGF-23 levels and non-SCD.

The current analyses suggest that non-SCD risk is elevated among the elderly with higher FGF-23 concentrations, particularly those with CKD. The incidence of SCD is elevated among the elderly with elevated FGF-23 levels and CKD. Although the FGF-23 and SCD risk attenuated substantially after adjustment for eGFR and ACR, the magnitude of association with SCD and non-SCD among the CKD subgroup was similar.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Survival curves for the association between FGF-23 quartiles and SCD

Figure 2.
Survival curves for the association between FGF-23 quartiles and non-SCD

Table 1

Baseline Characteristics by FGF-23 Quartile

	FGF-23 Q1 (<51 RU/mL)	FGF-23 Q2 (51-70 RU/mL)	FGF-23 Q3 (71-100 RU/mL)	FGF-23 Q4 (>100 RU/mL)
No. of Participants	825	820	807	792
Demographics				
Age (y)	77 ± 5	78 ± 5	78 ± 5	79 ± 5
Female sex	434 (53%)	468 (57%)	517 (64%)	527 (67%)
Black race	192 (23%)	122 (15%)	99 (12%)	114 (14%)
Prevalent CVD				
History of HF	27 (3%)	44 (5%)	60 (7%)	162 (20%)
History of MI	63 (8%)	62 (8%)	99 (12%)	134 (17%)
History of Stroke	44 (5%)	55 (7%)	40 (5%)	60 (8%)
CVD Risk Factors				
Hypertension	470 (57%)	502 (61%)	512 (64%)	546 (69%)
Diabetes	84 (10%)	111 (14%)	116 (14%)	163 (21%)
Current Smoker	42 (5%)	46 (6%)	78 (10%)	76 (10%)
BMI (kg/m ²)	26.3 ± 4.3	26.6 ± 4.2	27.3 ± 4.6	27.6 ± 5.3
Total cholesterol (mg/dL)	200 ± 37	202 ± 38	203 ± 41	202 ± 42
Lipid lowering medication	75 (9%)	84 (10%)	109 (14%)	106 (13%)
ECG parameters				
Atrial fibrillation	10 (1%)	8 (1%)	40 (5%)	74 (9%)
LVH	41 (5%)	37 (5%)	38 (5%)	70 (9%)
QT interval (ms)	422 ± 33	426 ± 36	421 ± 35	420 ± 39
LBBB	20 (2%)	17 (2%)	17 (2%)	29 (4%)
Kidney Function				
eGFR (ml/min/1.73m ²)	81±18	74±17	69±16	58 ±19
Urine ACR (mg/g)	6.9 [4.3-14.3]	8.4 [4.5-17.5]	8.3 [4.7-19.0]	13.4 [6.0-54.4]
eGFR <60 ml/min/1.73 m ² or ACR ≥30 mg/g n(%)	153 (19)	248 (30)	295 (37)	490 (62)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factor for cholesterol in mg/dL to mmol/L, ×0.02586.

Table 2

Association of FGF-23 with SCD and Non-SCD in the Cardiovascular Health Study

	Categorical Analysis				Linear model	
	FGF-23 Q1 (<51 RU/mL)	FGF-23 Q2 (51-70 RU/mL)	FGF-23 Q3 (71-100 RU/mL)	FGF-23 Q4 (>100 RU/mL)	Per Doubling of FGF-23	P§
SCD						
Annual event rate; no. events/no. at risk	0.3%; 22/825	0.4%; 25/820	0.5%; 32/807	0.7%; 39/792		
Unadjusted	1.00 (reference)	1.17 (0.66, 2.07)	1.58 (0.92, 2.72)	2.35 (1.39, 3.98)	1.39 (1.16, 1.67)	<0.001
Age, sex, race adjusted	1.00 (reference)	1.22 (0.69, 2.17)	1.72 (1.00, 2.98)	2.67 (1.56, 4.57)	1.46 (1.22, 1.75)	<0.001
+CVD risk factors [*]	1.00 (reference)	1.05 (0.59, 1.88)	1.39 (0.80, 2.42)	1.75 (1.00, 3.05)	1.26 (1.03, 1.54)	0.02
+Kidney function ^{**}	1.00 (reference)	0.95 (0.53, 1.70)	1.15 (0.65, 2.03)	1.16 (0.63, 2.14)	1.07 (0.85, 1.35)	0.6
Non-SCD						
Annual event rate; no. events/no. at risk	1.5%; 117/825	1.6%; 118/820	1.9%; 113/807	3.6%; 202/792		
Unadjusted	1.00 (reference)	1.05 (0.81, 1.36)	1.27 (0.99, 1.63)	2.59 (2.06, 3.27)	1.46 (1.35, 1.59)	<0.001
Age, sex, race adjusted	1.00 (reference)	1.07 (0.83, 1.39)	1.27 (0.98, 1.63)	2.58 (2.04, 3.26)	1.47 (1.36, 1.60)	<0.001
+CVD risk factors [*]	1.00 (reference)	0.97 (0.75, 1.25)	1.07 (0.83, 1.38)	1.95 (1.53, 2.48)	1.35 (1.23, 1.48)	<0.001
+Kidney function ^{**}	1.00 (reference)	0.91 (0.70, 1.18)	0.94 (0.73, 1.22)	1.41 (1.08, 1.84)	1.17 (1.06, 1.30)	0.003

Note: Unless otherwise indicated, values are given as hazard ratio (95% confidence interval).

ACR, albumin-creatinine ratio; CVD, cardiovascular disease; FGF-23, fibroblast growth factor 23; SCD, sudden cardiac death

^{*} p-value for interaction test between FGF-23 and CKD status was 0.49 for SCD and 0.02 for non-SCD.^{**} Adjusted for age, sex, race, diabetes, hypertension, congestive heart failure, myocardial infarction, smoking, and alcohol use, estimated glomerular filtration rate, and natural log(ACR).

Table 3

Association of FGF-23 levels (per doubling) with SCD and Non-SCD, Stratified by CKD^{*}

	Value	p-value
SCD		
Baseline CKD		
Annual event rate; total no. events/total no. at risk	0.77%; 63/1183	
Unadjusted	1.36 (1.06, 1.75)	0.02
Adjusted ^{**}	1.20 (0.89, 1.62)	0.2
No baseline CKD		
Annual event rate; total no. events/total no. at risk	0.30%; 55/2058	
Unadjusted	1.11 (0.79, 1.55)	0.6
Adjusted ^{**}	1.01 (0.69, 1.48)	0.9
Non-SCD		
Baseline CKD		
Annual event rate; total no. events/total no. at risk	3.6%; 305/1186	
Unadjusted	1.51 (1.35, 1.70)	<0.001
Adjusted ^{**}	1.26 (1.10, 1.45)	0.001
No baseline CKD		
Annual event rate; total no. events/total no. at risk	1.4%; 265/2058	
Unadjusted	1.09 (0.93, 1.28)	0.3
Adjusted ^{**}	1.02 (0.85, 1.22)	0.9

Unless otherwise indicated, values are given as hazard ratio (95% confidence interval).

jACR, albumin-creatinine ratio; CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; SCD, sudden cardiac death

^{*} p-value for interaction test between FGF-23 and CKD status was 0.49 for SCD and 0.02 for non-SCD.

^{**} Adjusted for age, sex, race, diabetes, hypertension, congestive heart failure, myocardial infarction, smoking, and alcohol use, estimated glomerular filtration rate, and natural log(ACR).